# Cholinoceptor - Activating &Cholinesterase-Inhibiting Drugs -2

# Mechanism of Action

- **increase** the concentration of endogenous **acetylcholine** at cholinoceptors.
- **Edrophonium** is a quaternary alcohols, bind **electrostatically and by hydrogen bonds** to the active site, thus preventing access of acetylcholine.
- The enzyme-inhibitor complex does not involve a covalent bond and is short-lived (on the order of 2–10 minutes).

- Carbamate esters, e.g., **neostigmine** and **physostigmine**. undergo a two-step hydrolysis sequence similler to acetylcholine.

- The covalent bond of the *carbamoylated* enzyme is more resistant to the second (hydration) process, and this step is correspondingly prolonged (**30 minutes to 6 hours**).

- The organophosphates. undergo initial binding and hydrolysis by the enzyme, resulting in a ***phosphorylated* active site**.

  The covalent phosphorus-enzyme bond is extremely stable and hydrolyzes in water at a very slow rate (hundreds of hours).

  After the initial binding-hydrolysis step, the phosphorylated enzyme complex may undergo a process called **aging.**

**Aging** involves the breaking of one of the oxygen-phosphorus bonds of the inhibitor and further strengthens the phosphorus-enzyme bond.

Aging occurs within 10 minutes with the chemical warfare agent, soman, and in 48 hours with the

agent, VX.

- **Pralidoxime** If given before aging has occurred, is able to break the phosphorus-enzyme bond and can be used as "**cholinesterase regenerator**" drugs for organophosphate insecticide poisoning.

# Organ System Effects

## Central Nervous System

- In **low concentrations**, the lipid-soluble cholinesterase inhibitors cause a subjective alerting response.
- **In higher concentrations**, they cause generalized **convulsions**, which may be followed by coma and respiratory arrest.

## Eye, Respiratory Tract, GIT, Urinary Tract

The effects are qualitatively similar to the effects of the direct-acting cholinomimetics.

## Cardiovascular System

**Mimic the effects of vagal nerve** activation on the heart.

Negative **chronotropic, dromotropic**, and **inotropic** effects and cardiac output falls.

The fall in cardiac output is due to bradycardia, decreased atrial contractility, and some reduction in ventricular contractility.

The latter effect occurs as a result of prejunctional inhibition of NE release.

Minimal effects by direct action on vascular smooth muscle because most vascular beds lack cholinergic innervations.

The *net* cardiovascular effects of moderate doses of cholinesterase inhibitors consist of:

modest bradycardia

a fall in cardiac output

an increased vascular resistance (**sympathetic ganglion stimulation**) that result in a rise in blood pressure.

## Neuromuscular Junction

- Low concentrations prolong and intensify the actions of Ach.

  This increases the strength of contraction, especially in muscles weakened by curare-like neuromuscular blockers or by myasthenia gravis.

- At higher concentrations fibrillation of muscle fibers. **Antidromic firing** (nerve impulses in a direction opposite to normal) of the motor neuron may also occur, resulting in fasciculations that involve an entire motor unit.

- With marked inhibition of acetylcholinesterase, **depolarizing neuromuscular blockade** occurs followed by a phase of **nondepolarizing blockade** as seen with **succinylcholine**

  (a depolarising neuromuscular blocker).

- Some quaternary carbamate cholinesterase inhibitors, e.g., **neostigmine**, have an additional *direct* nicotinic agonist effect at the neuromuscular junction.
- This may contribute to the effectiveness of these agents as therapy for myasthenia.

# Clinical Uses

## The Eye

- **Glaucoma** was treated with pilocarpine, methacholine, carbachol or ChEIs; physostigmine, demecarium, echothiophate, isoflurophate).
- These drugs have been replaced by **topical -ß-blockers** and **prostaglandin** derivatives.
- **Acute angle-closure glaucoma** is a medical emergency that usually requires **surgery.**
- Initial therapy consists of a combination of a direct muscarinic agonist and a cholinesterase inhibitor (e.g., pilocarpine plus physostigmine),

# GI and Urinary Tracts

**Clinic. Uses cont.**

- **Postoperative ileus** (atony or paralysis of the stomach or bowel following surgical manipulation) and **congenital megacolon**.

- **Urinary retention** postoperatively or postpartum or secondary to spinal cord injury or disease (neurogenic bladder).

- **Bethanechol** and **Neostigmine** are the most widely used, but it must be certain that there is no mechanical obstruction to outflow before using the cholinomimetic agents.

- **Pilocarpine**

  Has long been used to increase salivary secretion.

- **Cevimeline**

  A new direct-acting muscarinic agonist used for the treatment of dry mouth associated with Sjögren's syndrome (a systemic autoimmune disease) and that caused by radiation damage of the salivary glands.

# Neuromuscular Junction

**Myasthenia gravis** is an autoimmune disease affecting skeletal muscle neuromuscular junctions. **Antibodies** are detected in 85% of myasthenic patients.

The antibodies **reduce nicotinic receptor function**.

Frequent findings are ptosis, diplopia, difficulty in speaking & swallowing, and extremity weakness.


Severe disease may affect all the muscles, including those necessary for respiration.

- The disease resembles the neuromuscular paralysis produced by *d*-tubocurarine.
- Patients with myasthenia are very sensitive to the action of **neuromuscular blockers** and other drugs that interfere with neuromuscular transmission, e.g., aminoglycoside antibiotics.
- Patients with **ocular myasthenia** may be treated with cholinesterase inhibitors alone.
- Patients having more widespread muscle weakness are also treated with **immunosuppressant** drugs (steroids, cyclosporine, and azathioprine).
- In some patients, the **thymus** gland is removed.

## Clinic. Uses cont.

**Edrophonium** is used as a **diagnostic test** for myasthenia.

- A 2 mg dose is injected IV. If the patient has myasthenia gravis, an improvement in muscle strength that lasts 5 minutes can be observed.
- Edrophonium is also used to assess the adequacy of treatment with the longer-acting cholinesterase inhibitors in patients with myasthenia gravis.
- Clinical situations in which severe myasthenia (**myasthenic crisis**) must be distinguished from excessive drug therapy (**cholinergic crisis**).

## Clinic. Uses cont.

- Long-term therapy is usually accomplished with **pyridostigmine**; **neostigmine** or **ambenonium**.

- Muscarinic effects is controlled by **atropine**. Tolerance to the muscarinic effects develops, so atropine treatment is not required.

- Neuromuscular blockade is frequently produced as an adjunct to **surgical anesthesia**. After surgery, **neostigmine** and **edrophonium** are the drugs of choice used to **reverse this pharmacologic paralysis promptly**.

## Central Nervous System

- **Tacrine** is an anticholinesterase used for the treatment of mild to moderate **Alzheimer's disease**.

  Tacrine's efficacy is modest, and hepatic toxicity is significant.
- **Donepezil**, is newer, more selective used in treatment of cognitive dysfunction in **Alzheimer's** patients.
- Given once daily because of its long half-life, and it lacks the hepatotoxic effect of tacrine.

# Toxicity

- Varies markedly depending on their **absorption**, access to the CNS, and metabolism.
- **Direct-Acting Muscarinic Stimulants**
- **Pilocarpine** and the **choline esters** over dosage cause:

  **nausea, vomiting, diarrhea, urinary urgency, salivation, sweating, cutaneous vasodilation, and bronchial constriction.**

- The effects are all blocked competitively by **atropine**

**Certain mushrooms**

contain muscarinic alkaloids.

(*Amanita muscaria*, the first source of muscarine, contains very low concentrations of the alkaloid.)

Ingestion of these mushrooms causes typical signs of muscarinic excess

within 15–30 minutes.

Treatment is with **atropine**, 1–2 mg parenterally.

# Direct-Acting Nicotinic Stimulants

## Acute Toxicity

- The **fatal dose** of nicotine is 40 mg, or 1 drop of the pure liquid.

  This is the amount of nicotine in two regular cigarettes. Fortunately, most of the nicotine in cigarettes is destroyed by burning or escapes via the "side stream" smoke.

- Ingestion of nicotine insecticides or of tobacco by infants and children is usually followed by vomiting, limiting the amount of the alkaloid absorbed.

**Toxic effects of a large dose of nicotine are:**

(1) central stimulant actions, which cause convulsions and may progress to coma and respiratory arrest;

(2) skeletal muscle end plate depolarization, which may lead to depolarization blockade and respiratory paralysis.

(3) hypertension and cardiac arrhythmias.

Treatment of acute poisoning is symptom-directed.

- Muscarinic excess resulting from parasympathetic ganglion stimulation can be controlled with **atropine.**

- Central stimulation is treated with anticonvulsants such as **diazepam**. Neuromuscular blockade is not responsive to treatment and requires mechanical respiration.

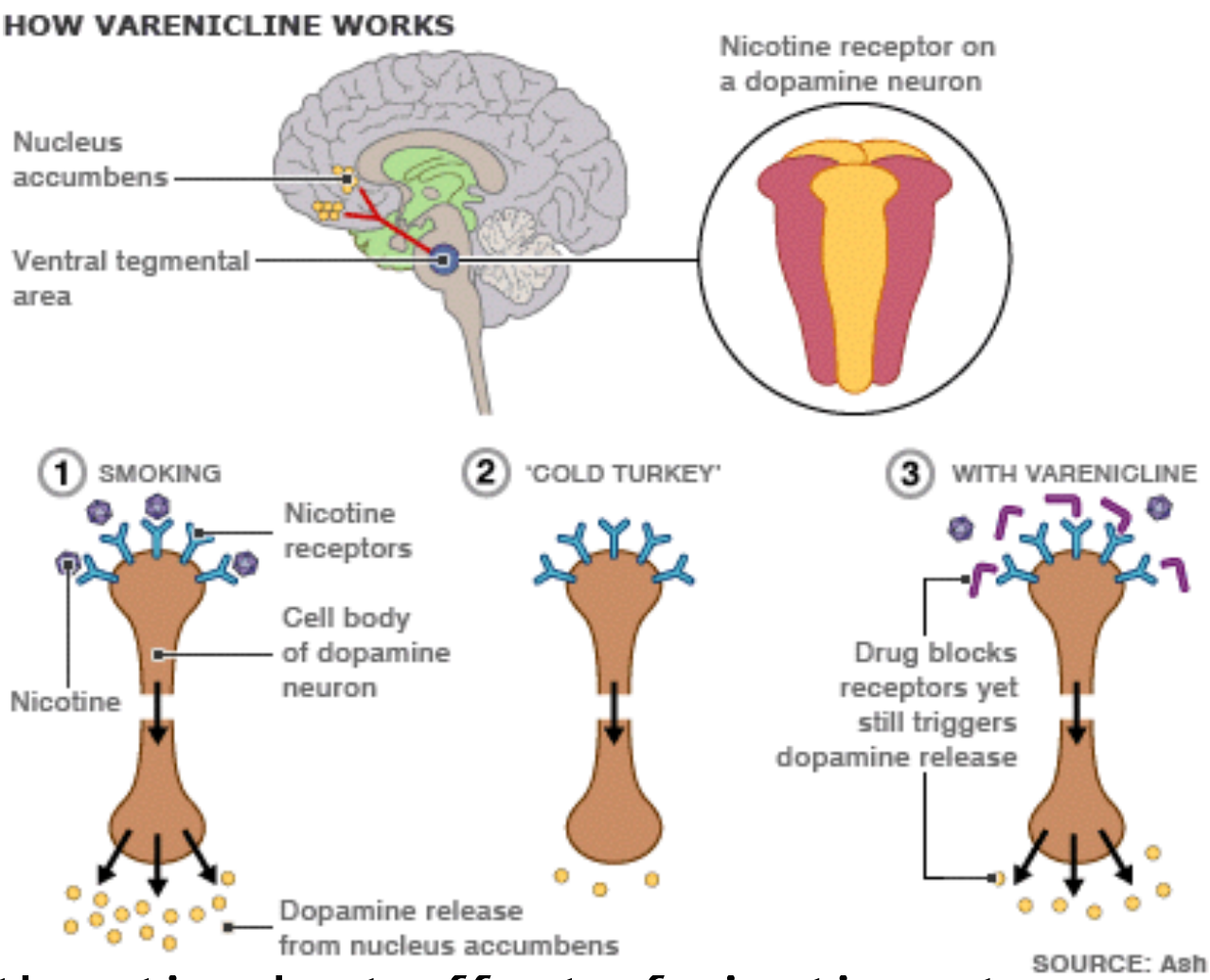
- Fortunately, nicotine is metabolized and excreted relatively rapidly. Patients who survive the first 4 hours usually recover completely if hypoxia and brain damage have not occurred.

## Chronic Nicotine Toxicity

- Nicotine contributes to the increased risk of **vascular disease and sudden coronary death associated with smoking**.
- Also, the high incidence of **ulcer recurrences** in smokers.
- **Replacement therapy with nicotine** in the form of gum, transdermal patch, nasal spray, or inhaler are used to help patients stop smoking.

**Varenicline**

- Has **partial agonist action at central nicotinic receptors.**
- **It also has antagonist properties** that persist because of its long half-life




- It prevents the stimulant effect of nicotine at presynaptic nicotinic receptors that cause release of dopamine.
- its use is limited by nausea and insomnia and also by exacerbation of psychiatric illnesses, including anxiety and depression.

## Cholinesterase Inhibitors

- The major source of intoxications is **pesticide**.
- **pesticides** can cause symptoms which persist for days.
- chemical warfare agents (**soman, sarin, VX**) induce effects rapidly.
- **Miosis, salivation, sweating, bronchial constriction, vomiting, and diarrhea**.

  CNS involvement (**cognitive disturbances, convulsions, and coma**) usually follows rapidly, accompanied by peripheral nicotinic effects, especially depolarizing neuromuscular blockade.

**Therapy always includes:**

(**1**) maintenance of vital signs—respiration in particular may be impaired.

(**2**) decontamination to prevent further absorption.

(**3**) atropine parenterally in large doses, given as often as required to control muscarinic excess.

Therapy often also includes treatment with pralidoxime, and benzodiazepines for seizures.

- **Preventive therapy for cholinesterase inhibitors warfare agents**
- Personnel are given **autoinjection syringes containing pyridostigmine and atropine**.

- **Chronic exposure** to certain organophosphate compounds causes **delayed neuropathy associated with demyelination of axons.**
- The effects are not caused by cholinesterase inhibition but rather by neuropathy target esterase (NTE) inhibition whose symptoms (weakness of upper and lower extremities, unsteady gait) appear 1–2 weeks after exposure.

- **Another nerve toxicity called intermediate syndrome** occurs 1–4 days after exposure to organophosphate insecticides. This syndrome is also characterized by muscle weakness; its origin is not known but it appears to be related to cholinesterase inhibition.